Remarks

Claims 101-110 are pending in the application and stand rejected. Claims 101-110 are canceled, and new claims 111-113 have been added. These new claims specify that the composition comprises (i) a delivery agent *consisting essentially of* at least one cationic peptide and (ii) an RNAi agent selected from the group consisting of siRNA, shRNA, *and microRNA*. Support for microRNAs can be found in paragraph 66.

No new matter has been added by the present Amendment. Applicant specifically reserves the right to pursue the subject matter of the canceled or amended claims in a related application. The present Amendment is introduced for the *sole* purpose of furthering prosecution. Applicant respectfully requests reexamination and reconsideration of the case in light of the present Amendment and the following Remarks. Each of the rejections levied in the Office Action is addressed individually below.

Rejections under 35 U.S.C. § 103(a) as allegedly being obvious

Claims 101-110 stand rejected under 35 U.S.C. § 103(a) on the ground that they are unpatentable over Abe *et al.* (2001, *Eur. J. Pharm. Sci.*, 13:61-69), Tuschl *et al.* (PCT Patent Publication WO 02/44321), Astriab-Fisher *et al.* (2000, *Biochem. Pharmacol.*, 60:83-90), Lewis *et al.* (US Patent Publication 2003/0125281), as evidenced by Caplen (2003, *Expert Opin. Biol. Ther.*, 3:575-86) and Trubetskoy *et al.* (US Patent Publication 2004/0162235).

The Examiner cites Abe as teaching use of antisense oligonucleotides which target the influenza virus nucleoprotein (NP) gene, but acknowledges that Abe does not teach use of an siRNA targeted to the NP gene or use of siRNA along with a cationic peptide. The Examiner alleges that the other cited references remedy these defects. In particular, the Examiner states that Tuschl teaches that siRNA is a more effective and safe alternative to antisense technology, that Astriab-Fischer teach inhibition of gene expression using antisense oligonucleotides conjugated to cationic peptides, and that Lewis teaches compositions comprising siRNA and delivery agents such as polycation agents. The Examiner strings together the pieces of these individual teachings to conclude that it would have been obvious to one of ordinary skill in the art to use a cationic peptide for delivery of an influenza siRNA into cells, as recited in the present claims. Applicant respectfully disagrees and respectfully submits that the teachings of

these references when considered *as a whole* do not lead one of ordinary skill in the art to the present claims.

First, although one of ordinary skill in the art may have been motivated to substitute RNAi technology for antisense technology, one of ordinary skill would *not necessarily* have been motivated to utilize the same *delivery methods* for both technologies. Indeed, one of ordinary skill in the art would have understood that antisense oligonucleotide technology utilizes nucleic acids having different structures than does RNAi technology. In particular, antisense oligonucleotide technology utilizes *single-stranded DNA molecules*, whereas RNAi technology utilizes *double-stranded RNA molecules*. One of ordinary skill in the art certainly would have appreciated that (1) DNA and RNA molecules and (2) single-stranded and double-stranded nucleic acids have very different chemical properties and behaviors from one another. Thus, one of ordinary skill in the art would not expect compounds that might be useful for delivery of a single-stranded DNA molecule to be effective for delivery of a double-stranded RNA molecule.

Indeed, the specification acknowledges the challenges that one of ordinary skill in the art might expect from an attempt to use cationic peptides for delivery of RNAi agents. For example, the specification states that "[t]he ability of cationic polymers to promote cellular uptake of DNA is thought to arise partly from their ability to bind to DNA and condense large plasmid DNA molecules into smaller DNA/polymer complexes for more efficient endocytosis" (paragraphs 113 and 195). Thus, the specification describes that, at the time when the invention was filed, those of ordinary skill in the art recognized that cationic polymers were effective because they bound to and condensed (1) *large* (2) *DNA* molecules. In contrast, siRNA, shRNA, and miRNAs are *RNA* molecules, and are *small*. Indeed, the specification explains that "siRNA duplexes are short (e.g., only approximately 19-21 nucleotides in length), suggesting that they probably cannot be condensed much further" (paragraph 195). Thus, those of ordinary skill in the art at the time when the invention was filed might have expected that these different kinds of molecules having different chemical and structural properties would behave differently if delivery of these molecules were to be attempted. Indeed, one of ordinary skill in the art certainly had reasons to *doubt* that cationic polymers, much less cationic *peptides*, would be effective for delivery of small RNA agents, as recited in the claims.

Moreover, the Examiner cites Lewis *et al.* as providing the "missing link" between (1) cationic polymers as delivery agents for (2) RNAi agents. Indeed, Lewis is the *only* cited reference that relates to *both* small RNA molecules *and* cationic polymers. Applicant notes, however, that Lewis actually *teaches away* from the compositions recited in the claims for at least two reasons. First, Lewis teaches away from compositions that comprise cationic *peptides*, as recited in the claims. Although Lewis describes compositions that comprise polycations, and mentions that the polycations *can be* cationic peptides such as polylysine (paragraph 11), Lewis further explains that "[p]olylysine induces anaphylactic shock and is very immunogenic" (paragraph 11). Indeed, the bulk of the description of polycations in Lewis relates to *other* cationic polymers that do not have these undesirable effects. By describing several disadvantages of using cationic peptides, Lewis, in fact, *teaches away* from use of cationic *peptides*, as recited in the present claims.

Second, Lewis teaches away from compositions that comprise a delivery agent *consisting essentially of* at least one cationic peptide, as recited in the claims. In particular, Lewis teaches an siRNA delivery agent that contains *two different compounds* – a polycation, *and* an amphipathic compound (see the title of the application and the entire specification, *e.g.*, paragraphs 9, 16, 19, 20, and 173). In contrast, the present claims recite compositions that comprise an RNAi agent and a delivery agent *consisting essentially of* at least one cationic peptide.

Indeed, Lewis explains that it is, in fact, *crucial* to include *both* the amphipathic compound *and* the polycation in order to effectively deliver siRNAs. For example, Lewis states that "the use of a polycation and a novel amphipathic compound *together* significantly increased siRNA transfer efficiency" (paragraph 10; emphasis added). Lewis further explains that:

> "most of the novel amphipathic compounds . . . *do not efficiently mediate the transfer of genes into cells when used alone*. However, the use of polycations with these novel amphipathic cationic compounds enables the efficient gene transfer into a variety of animal cells with minimal cellular toxicity. The *combination* of polycation and amphipathic compounds *enhances the efficiency* of siRNA delivery" (paragraph 19; emphasis added).

Moreover, one of the experiments presented in the Examples shows that addition of an amphipathic compound "*significantly enhances delivery* of siRNA when combined with ePEI" (*i.e.*, polyethyleneimine, which, notably, is a cationic *polymer*, not a cationic *peptide*) (paragraph 179; emphasis added; see also Table A).

Thus, Lewis teaches (1) that the *combination* of cationic polymer + amphipathic compound is crucial for efficient delivery of siRNA, and (2) that there are disadvantages to using a cationic *peptide* as the cationic polymer in the Lewis compositions. In contrast, the present claims recite compositions comprising an RNAi agent and a delivery agent consisting essentially of at least one cationic peptide.

Applicant, therefore, respectfully submits that no combination of the cited references would lead one of ordinary skill in the art to the present claims. Indeed, one of ordinary skill in the art would have no reasonable expectation of success in using cationic peptides for delivery of *short* nucleic acids that are *RNA* molecules. Moreover, the Lewis reference, upon which the Examiner relies to pin together the various individual teachings of the other cited references, actually *teaches away* from the present claims. Applicant, therefore, respectfully submits that the claims are not obvious over the cited references, and respectfully requests that the rejection be removed.

Obviousness-Type Double Patenting

The Examiner has levied a *provisional* obviousness-type double patenting rejection, asserting that claims 101-110 pending in the present application are not patentably distinct from claims 12, 22, and 24-27 of co-pending U.S. application U.S.S.N. 11/259,434. Applicant respectfully refrains from commenting on this rejection until such time as it matures into an *actual* rejection.

Conclusion

For all of the reasons set forth above, each of the rejections in this case should be removed and the application should proceed to allowance. A Notice to that effect is requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience.

Respectfully submitted,

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